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Prevalence and patterns of antidepressant switching amongst Primary Care patients in the UK

Authors

Becky Mars (PhD)[1], Jon Heron (PhD)[1], David Gunnell (PhD)[1], Richard M Martin (PhD)[1], Kyla H Thomas (PhD)[1] and David Kessler (MD, MRCGP) [1]

[1] School of Social and Community Medicine, University of Bristol, Bristol, UK

***Corresponding author details**

Senior Research Associate in Epidemiology

Centre for Academic Mental Health

School of Social and Community Medicine

University of Bristol

Oakfield House

Bristol

BS8 2BN

Email: becky.mars@bristol.ac.uk

Telephone Number: (0117) 3310165

Abstract

Objective: Non-response to antidepressant treatment is a substantial problem in Primary Care, and many patients with depression require additional second-line treatments. This study aimed to examine the prevalence and patterns of antidepressant switching in the UK, and identify associated demographic and clinical factors.

Method: Cohort analysis of antidepressant prescribing data from the Clinical Practice Research Datalink; a large, anonymised, UK primary care database. The sample included 262,844 patients who initiated antidepressant therapy between 1st January 2005 and 31st June 2011.

Results: 9.3% of patients switched to a different antidepressant product, with most switches (60%) occurring within eight weeks of the index date. The proportion switching was similar for SSRIs, TCAs and other antidepressants (9.3%, 9.8% and 9.2% respectively). Most switches were to an SSRI (64.5%), and this was the preferred option regardless of initial antidepressant class. Factors predictive of switching included male gender, younger (<18 years) and older age (>60 years), and history of self-harm and psychiatric illness.

Conclusion:

Over one in every eleven patients who initiates antidepressant therapy will switch medication, suggesting that initial antidepressant treatment has been unsatisfactory. Evidence to guide choice of second-line treatment for individual patients is currently limited. Additional research comparing different pharmacological and psychological second-line treatment strategies is required In order to inform guidelines, and improve patient outcomes.

Keywords: CPRD; Antidepressants; General practice; Switching; Primary care; Depression

Introduction

Major Depressive Disorder is a common psychiatric disorder, and is among the leading causes of disability worldwide (Ferrari et al., 2013). Guidelines from the National Institute for Health and Clinical Excellence, (NICE) in the UK (National Institute for Health and Clinical Excellence, 2009) highlight the importance of adequate treatment duration, and recommend that antidepressants (ADs) should be continued for at least six months following remission to reduce risk of relapse. Guidelines in America suggest a similar period of 4-9 months (American Psychiatric Association, 2010). However, a substantial proportion of patients discontinue AD treatment before this. Common reasons for early discontinuation include lack of efficacy and intolerance (Mitchell and Selmes, 2007, Thomas et al., 2013c, Fava, 2000, Linden et al., 2000).

Non-response to AD treatment is common in UK Primary Care, with 55% of patients not responding to medication despite adequate dose and duration of treatment (Thomas et al., 2013c). Findings from clinical trials suggest that for many patients, remission is not achieved with monotherapy alone, and additional second-step treatments are often required (Rush et al., 2006, Huynh and McIntyre, 2008). Switching to another AD can improve remission rates, for example in the STAR*D trial, approximately 1 in 4 patients who did not respond/were intolerant to an initial SSRI treatment achieved remission after switching ADs (Rush et al., 2006, Huynh and McIntyre, 2008).

Reported switching rates from existing studies range from 8% to 40% (Milea et al., 2010, Wu et al., 2013, Saragoussi et al., 2012, Andersson Sundell et al., 2013, Marcus et al., 2009, Ball et al., 2014, Schultz and Joish, 2009), and there is some evidence to suggest that the likelihood of switching may be influenced by demographic and clinical factors such as age, gender, history of /current psychiatric disorder, and severity of depression (Milea et al., 2010, Saragoussi et al., 2012, Marcus et al., 2009). However, the level and pattern of AD switching amongst Primary Care patients in the UK remains poorly understood. A better understanding of the products that demonstrate high levels of

switching would be of benefit, as this may be indicative of poor response or tolerability, and could inform guidance on initial AD choice.

This paper examines switching patterns of ADs amongst patients who initiated treatment between 1995 and 2011, using data extracted from the Clinical Practice Research Datalink (CPRD); a large, anonymised, Primary Care database in the UK. Our objectives were to:

1. Describe patterns of AD switching according to product type and drug class
2. Examine demographic characteristics and clinical factors associated with AD switching, including age, gender and psychiatric illness.

Methods

Data source

The Clinical Practice Research Datalink (CPRD) (www.cprd.com) is one of the largest primary care databases in the world and contains anonymised electronic records from over 4 million active patients, representing about 6.9% of the UK population (Herrett et al., 2015). The database contains information on diagnosis, symptoms, prescriptions, referrals and test results, as well as demographic and administrative information. This information is routinely entered by GPs and their staff onto their computer systems, and then is extracted, anonymised and quality checked. The patient population captured in the database is representative of the overall UK population in terms of age, sex and ethnicity (Herrett et al., 2015). The MHRA Independent Scientific Advisory Committee (ISAC) reviewed the study protocol for scientific quality (protocol #: 15_100). The CPRD group has obtained ethics approval from a multicentre research ethics committee for all purely observational research using CPRD data- that is, studies that do not include patient involvement and are anonymised.

Study population

All patients who initiated AD treatment between 1st January 2005 and 31st June 2011 were identified. The date of their first antidepressant prescription during this time period was defined as the index date. Analyses were restricted to 'acceptable' patient records from practices that met the CPRD quality criteria and contributed data for the entire study period (Herrett et al., 2015). To ensure patients were newly started on AD treatment, they were required to be registered with a CPRD contributing practice for at least 3 years before the index date, without an AD prescription during this time. Continuous registration for at least 6 months following the index date was also required, to ensure there was sufficient time for a treatment switch. Patients were excluded if they were <14 years of age or if they initiated treatment with more than one AD.

Treatment change

Only the first AD treatment episode was considered. The intended duration of treatment was estimated from the dosing instructions and the quantity prescribed. Where no dosage instructions were provided, the median for the product type was used. Consecutive prescriptions were considered to be part of the same treatment episode if the gap between the expected end of one prescription and the start of another was 30 days or less.

A switch in AD medication was defined as a discontinuation of the index (or first-line) AD, and prescription of a new (second-line) AD within 30 days of the presumed end date of the first line treatment, and, no overlap of the two drugs for more than 30 days. Patients who had a change in AD treatment together with a consecutive repeat prescription of the index AD were categorised as augmentation rather than a treatment switch. Patients were also categorised as augmentation if there was an overlap of the two AD drugs for >30 days. Where more than one switch occurred during the same treatment episode, we focused on the first switch only.

Analysis strategy

AD medications were identified using section 4.3. of the British National Formulary, and classified into three categories based on their proposed method of action (Appendix 1): Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic antidepressants (TCAs), and 'other' antidepressants, largely consisting of Mirtazapine and Venlafaxine. Prescriptions of Amitriptyline (<75mg) and Nortriptyline were excluded, as has been done previously (Marcus et al., 2009), as they are commonly prescribed for indications other than depression, particularly pain (Ilyas and Moncrieff, 2012, Noordam et al., 2015). However sensitivity analysis including these medications was also conducted.

The proportion of patients who switched AD and the proportion augmenting first-line treatment with a second AD product were calculated. As the focus of this paper is on AD switching AD augmentation was not investigated further. The pattern of AD switching was examined according to

both individual product type and AD class. Descriptive analysis of first and second line AD were performed using summary statistics (percentages for categorical variables and median for continuous variables). Primary analysis used univariable logistic regression models to investigate the association between switching and a number of patient demographic and clinical characteristics, including age and sex, and lifetime history of self-harm, any psychiatric illness, and depression and anxiety specifically. As decisions regarding AD choice may be particularly influenced by recent self-harm history, we also examined associations with past year self-harm. Secondary analysis was also conducted i) adjusting for age and gender, and ii) additionally adjusting for psychiatric problems, in order to explore whether associations were independent of these factors. Psychiatric illness and self-harm were identified in CPRD using Read Codes (Thomas et al., 2013a, Davies et al., 2013, Thomas et al., 2013b) which are available on request from the authors. Read codes are a coded thesaurus of clinical terms used in General Practice in the United Kingdom. They provide the standard vocabulary by which clinicians can record patient findings and procedures in IT systems across primary and secondary care (Health & Social Care Information Centre).

Results

The final sample eligible for analysis included 262,844 patients (94,280 males, 168,564 females, mean age at index date 47.8 years) from 419 GP practices. Table 1 shows the pattern of AD prescribing according to AD product and drug class. The majority (86.9%) were prescribed an SSRI as the index AD, 6.3% were prescribed a TCA, and 6.8% another AD. The most common ADs prescribed as a first-line treatment were Citalopram (48.5%) and Fluoxetine (26.0%), which together accounted for 74.5% of all index ADs. In total, 24,471 (9.3%) of patients who initiated AD treatment switched to another AD. The number of patients who augmented AD treatment with a second AD was 4,630 (1.8%).

The total proportion of patients who switched AD was similar for each of the three classes investigated; 9.8% of those prescribed a TCA, 9.3% of those prescribed an SSRI and 9.2% of those prescribed another AD. The median time to treatment change was 44 days (interquartile range 22 days, 98 days). The time to switch was slightly longer amongst those prescribed an SSRI than a TCA or other AD (45, 38, and 35 days respectively). Around a quarter of the sample (24.4%) switched AD within the time frame recommended by the NICE guidelines (4-8 weeks); 35.5% switched AD before 4 weeks and 40.1% after 8 weeks.

Nearly two thirds of AD switches were to an SSRI (64.5%), 24.8% switched to the "other AD" class and 10.7% to a TCA. A switch to an SSRI was the most frequent pattern, regardless of the index drug (Table 2), however this was proportionately more common amongst those prescribed another AD (80.2% of switches from this drug class) or a TCA (75.4%), than from those prescribed an SSRI (62.4%) (Figure 1). The most common ADs prescribed as a second-line treatment were Citalopram (25.8% of those who switched AD), Fluoxetine (17.5%), Mirtazapine (16.2%) and Sertraline (13.0%). The ten most common switching patterns, accounting for almost two-thirds of all AD switches, are shown in supplementary Table 1.

Characteristics associated with switching

The demographic and clinical factors associated with AD switching are shown in Table 3.

1) Gender: The odds of switching AD were 21% higher amongst males than females (OR 1.21, 95% CI 1.18, 1.24; 8.7% of females switched AD compared with 10.4% of males). Effect estimates were similar when adjusting for age and history of psychiatric illness (Supplementary Table 2). Females were somewhat more likely to be prescribed a TCA as the index AD than males (8.1% vs. 2.9%), however the overall pattern of switching between ADs was similar across genders (results available on request).

2) Age: The proportion of patients switching ADs was similar for those aged 18-30, 31-35 and 46-60 (9.6%, 9.8%, and 9.6% respectively). Switching was relatively less common amongst the youngest, and older age categories when compared with the 31-45 year reference group [OR range 0.66- 0.91}. Effect estimates were similar when adjusting for gender and history of psychiatric illness (Supplementary Table 2). There was a negative association between having an SSRI as the index AD and age (77.5% of those aged 76+, compared to over 90.3% in those aged <45 years).

3) Clinical characteristics: Patients were more likely to switch AD if they had a lifetime, or past year history of self-harm [lifetime: OR 1.49, 95% CI 1.42, 1.56; past year OR 1.21, 95% CI 1.07, 1.37], or a history of psychiatric illness [OR 2.06, 95% CI 1.99, 2.13], depression [OR 1.92, 95% CI 1.86, 1.98] or anxiety [OR 1.54, 95% CI 1.50, 1.59]. Effect estimates were similar when adjusting for age and gender (Supplementary Table 2).There was little difference in first line AD according to lifetime history of anxiety or self-harm however those who had self-harmed in the past year were less likely than those without recent self-harm to initiate AD treatment with a TCA (2.6% vs 6.3%). Those with psychiatric illness or depression were more likely than those without to initiate treatment with an SSRI, and less likely to be prescribed a TCA or other AD.

Sensitivity analysis

We conducted additional sensitivity analysis including prescriptions of low dose Amitriptyline or Nortriptyline. When including these medications, there was a considerable increase in the proportion of patients prescribed a TCA as the index AD (rising from 6.3% of index prescriptions to 31.1%). Amitriptyline or Nortriptyline together accounted for 27.8% of all index AD prescriptions and 89.1% of TCAs. SSRI prescriptions accounted for 64.2% of index ADs and other ADs accounted for 4.7%.

The total proportion of patients who switched AD decreased slightly from 9.3% to 7.8%. This was largely driven by a reduction in switching amongst those prescribed a TCA (from 9.8% to 3.9%), as results for SSRIs and other ADs were similar to the main analysis (9.6% and 9.7%). The proportion of patients who switched to a TCA as a second line treatment increased from 10.7% to 16.9%. Amitriptyline or Nortriptyline together accounted for 7.5% of second line ADs.

Discussion

Summary of main results

We found that 9.3% of people prescribed an AD switched to a different AD product during their index treatment episode, indicating that initial AD treatment was likely unsatisfactory. Levels of switching were similar amongst those prescribed an SSRI, a TCA or other AD. In line with NICE guidelines (National Institute for Health and Clinical Excellence, 2009), we found that SSRIs accounted for the majority of first line, and second line treatments, although there was a higher representation of non-SSRI treatment post-switch. Characteristics associated with switching included male gender, younger and older age (compared with reference 31-45 year age group), lifetime history of self-harm, psychiatric illness, anxiety and depression.

Strengths and weaknesses

As far as we are aware, this is the first UK study to examine switching patterns in detail since the introduction of the 2004 NICE guidelines. Findings from studies conducted prior to this (Saragoussi et al., 2012, Martin et al., 1997) are based on data collected prior to 2004, and are likely to be less relevant to current clinical practice. The main strength of our study is the database from which the data were extracted. The CPRD is a large anonymised database of Primary Care Patients, which allowed us to examine AD switching according to individual product and class, as well as investigate a range of associated factors. The database provides valuable information about longitudinal treatment course from patients collected in a real-life setting. In order to ensure patients were newly started on AD they were required to have a minimum AD-free period of three years prior to their index date. Whist this could result in some patients being included who have previously had AD treatment (i.e. recurrent users rather than new starters), our exclusion period is much longer than many other studies, which have typically required an AD-free period of only 6 months-1 year. We also did not restrict the period of follow-up, which allowed switching to be examined across the whole of the first treatment episode.

Findings must also be interpreted in light of several limitations. Firstly, our analysis is based on prescriptions issued in Primary Care, and we do not have information about those issued in other settings (e.g. hospital outpatients). However, the vast majority of depressed patients are treated in Primary Care (Tylee and Jones, 2005, Barkil-Oteo, 2013).. We also do not have information about the dispensing of medications or patient compliance. Secondly, we do not have data on drug efficacy, or tolerance, and so it was not possible to establish the reason for the AD switch, or whether this differed according to AD product. This is an important area for future research. Thirdly, whilst the CPRD is representative of UK general practices in terms of age, sex and ethnicity, it may not be not be representative with regards to practice size or geographical distribution (Herrett et al., 2015). There may also be variability across patients/practices regarding completeness of data and in the coding of diagnosis. Moreover, if a GP has entered diagnostic information as free text, rather than using a read code, then this information would likely be missed. It is also not possible within CPRD to identify the indication for a given medication prescription. Fourthly, data is only available to 2011, however, the latest guidelines were released in 2009, and so results are likely to be applicable to recent clinical practice. Finally, the focus of this paper was on AD switching and we did not examine other potential treatment patterns such as combination or augmentation treatments, or switching to psychotherapy.

Comparison with previous literature

The rate of switching reported in previous studies has varied considerably from 8% to 40% (Milea et al., 2010, Wu et al., 2013, Saragoussi et al., 2012, Andersson Sundell et al., 2013, Ball et al., 2014, Marcus et al., 2009, Schultz and Joish, 2009). Methodological differences in study population and design make direct comparisons with previous research difficult. Results may be influenced by many factors including i) the definition of a treatment switch, ii) the length of follow-up, iii) the length of pre-index AD free period, iv) the time period studied, v) inclusion criteria e.g. depression diagnosis, vi) differences in healthcare across countries, vii) sample source/database, and viii) the

number/type of ADs included in the analysis (see Supplementary Table 3 for a comparison of studies).

In this study, the proportion of patients who switched AD was approximately equal across the AD classes. This is inconsistent with previous research suggesting that SSRIs are better tolerated (Barbui et al., 2000, Cipriani et al., 2009, Qin et al., 2014, Von Wolff et al., 2013) (and therefore would be thought to be less likely to be switched) than other ADs. However, the proportion of 'early switchers' was somewhat lower for those prescribed an SSRI compared with those prescribed a TCA or other AD, which could indicate that switches from SSRIs were more likely to be due to lack of efficacy, than to unwanted side effects. Our findings are also inconsistent with some previous studies that have found higher rates of switching amongst those prescribed a TCA (Milea et al., 2010, Saragoussi et al., 2012, Marcus et al., 2009, Wu et al., 2013, Sheehan et al., 2008), with one study reporting particularly high switching rates for Amitriptyline (Saragoussi et al., 2012). We excluded Amitriptyline and Nortriptyline from the main analysis, as they are commonly prescribed for indications other than depression (Ilyas and Moncrieff, 2012, Noordam et al., 2015, Marcus et al., 2009). Sensitivity analysis found that rates of switching actually decreased when including these medications. We also found high rates of switching for Lofepramine (18.7%), suggesting that this TCA may be less effective/less well tolerated compared to other AD medications.

Few studies have examined the longitudinal course of treatment including detailed descriptive information on both first and second-line ADs. Our findings are consistent with previous research showing that SSRIs are the preferred index AD, and that a switch to an SSRI is the most common pattern (Milea et al., 2010, Saragoussi et al., 2012, Andersson Sundell et al., 2013, Marcus et al., 2009). Prescriptions of an SSRI as a second-line treatment were comparatively lower, particularly when switching from another SSRI (Milea et al., 2010, Saragoussi et al., 2012). This could suggest that some GPs have a preference for switching to an AD with a different mechanism of action. Findings from the STAR*D study (Rush et al., 2006, Huynh and McIntyre, 2008) fail to support this view, and suggest that remission rates and adverse effects are similar for those who switch

between and within classes. However overall the evidence is limited and other trials have found that a switch to Venlafaxine after an SSRI failure appears to offer some benefit over a second SSRI (Connolly and Thase, 2011, Ruhé et al., 2006). Only 5.6% of patients in this sample who switched AD switched to Venlafaxine.

Most switches occurred within eight weeks (60%) of the index date, with a median time to switch of 44 days. This is consistent with current guidelines which recommend switching within 4-8 weeks, depending on initial response. It is also comparable to a recent US study which reported a median switch time of 42 days (Milea et al., 2010). We found that switching was less likely amongst females and amongst the younger (<18) and older (>65) age groups. The association with gender (Saragoussi et al., 2012, Marcus et al., 2009) and older age has also been reported in other studies (Milea et al., 2010, Saragoussi et al., 2012, Mullins et al., 2005), although not all findings for age have been consistent (Marcus et al., 2009). One hypothesis is that increasing age is associated with increasing compliance with treatment (Rolnick et al., 2013, Akincigil et al., 2007), or that older people may be prescribed lower doses, which may limit side effects. Younger people may be less likely to switch as alternative ADs are limited in this age group (the only AD recommended by the NICE guidelines is fluoxetine (National Institute for Health and Care Excellence, 2015)). The finding that switching was more common in males requires further exploration but could potentially reflect differences in the profile of adverse effects.

Switching was also associated with lifetime history of self-harm, psychiatric illness, depression and anxiety. These findings are in line with previous research suggesting that switching is more common amongst patients who present with a more severe clinical profile (Milea et al., 2010, Saragoussi et al., 2012, Marcus et al., 2009). It is possible that patients presenting with more severe depression, or comorbidities have a reduced likelihood of response to initial monotherapy. Those with recent (but not lifetime) self-harm were less likely to initiate treatment with a TCA. This is in line with guidance which highlight the need to consider toxicity in those at risk of suicide as TCAs are more toxic in overdose. It is also notable that Dosulepin was prescribed both as a first-line and a

second-line treatment (albeit to a small proportion of patients), as this mediation is contraindicated due to its toxicity in overdose and increased cardiac risk (National Institute for Health and Clinical Excellence, 2009) .

Future directions and clinical implications

Non-response to AD treatment is a substantial problem in Primary Care (Thomas et al., 2013c); many patients with depression do not achieve remission with monotherapy, and require additional interventions. Further research is needed comparing different pharmacological and psychological second-line treatment strategies including switching, combination and augmentation treatment, in order to inform guidelines and improve patient outcomes.

When switching AD, UK treatment guidelines suggest switching to another SSRI, or to a better-tolerated newer-generation AD such as Mirtazapine (National Institute for Health and Clinical Excellence, 2009). However, the evidence to support best practice in this area is currently very limited; few high-quality RCTs have investigated the efficacy of switching antidepressants (Connolly and Thase, 2011, Anderson et al., 2008) and results have not been consistent. Moreover, findings from clinical trials may not generalise to routine clinical practice and so additional studies are needed which build on the work from this study, and examine AD switching in real-life settings. More research is also needed exploring the reasons why patients switch medications, and the impact this may have on their treatment and outcome.

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Competing interests

The authors declare that there is no conflict of interest.

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Table 1: Antidepressant switch according to product

AD product [a]	First-line AD (% of total sample)	Number who switched (% of index drug)	median time to switch, days (IQ range)	Number switched within recommended time frame (4-8 weeks)	Early switchers (<4 weeks)	Late switchers (>8 weeks)	Second line AD (% of those who switched)
TCAs							
Amitriptyline hydrochloride	2509 (1.0%)	171 (6.8%)	63 (23,183)	27 (15.8%)	52 (30.4%)	92 (53.8%)	130 (0.5%)
Dosulepin hydrochloride	6,821 (2.6%)	624 (9.1%)	38 (21, 75)	175 (28.0%)	247 (39.6%)	202 (32.4%)	876 (3.6%)
Imipramine hydrochloride	1185 (0.5%)	63 (5.3%)	49 (29, 84)	24 (38.1%)	15 (23.8%)	24 (23.8%)	78 (0.3%)
Lofepramine	1,494 (0.6%)	280 (18.7%)	35 (21, 67)	79 (28.2%)	119 (42.5%)	82 (29.3%)	739 (3.0%)
Trazodone hydrochloride	2,795 (1.1%)	296 (10.8%)	36 (18, 74)	69 (23.3%)	126 (42.6%)	101 (34.1%)	597 (2.4%)
Other TCAs	1,711 (0.7%)	171 (10.0%)	34 (14, 96)	34 (19.9%)	78 (45.6%)	59 (34.5%)	207 (0.8%)
Total TCAs	16,453 (6.3%)	1,605 (9.8%)	38 (21, 83)	408 (25.4%)	637 (39.7%)	560 (34.9%)	2627 (10.7%)
SSRIs							
Citalopram hydrobromide/ Citalopram hydrochloride	127,458 (48.5%)	10,401 (8.2%)	46 (22, 105)	2,437 (23.4%)	3,583 (34.5%)	4,381 (42.1%)	6,310 (25.8%)
Escitalopram oxalate	12,523 (4.8%)	1,443 (11.5%)	63 (28, 210)	288 (20.0%)	392 (27.2%)	763 (52.3%)	1,433 (5.9%)
Fluoxetine hydrochloride	68,442 (26.0%)	7,353 (10.7%)	43 (23, 90)	1,963 (26.7%)	2,537 (34.5%)	2,853 (38.8%)	4,271 (17.5%)
Paroxetine hydrochloride	3,681 (1.4%)	416 (11.3%)	36 (20, 84)	108 (26.0%)	162 (38.9%)	146 (35.1%)	559 (2.3%)
Sertraline hydrochloride	16,295 (6.2%)	1,591 (9.8%)	39 (19, 84)	355 (22.3%)	665 (41.8%)	571 (35.9%)	3,183 (13.0%)
Other SSRIs (fluvoxamine maleate)	53 (<0.1%)	4 (7.5%)	164 (40, 306)	0 (0%)	1 (25.0%)	3 (75.0%)	19 (0.1%)
Total SSRIs	228,452 (86.9%)	21,208 (9.3%)	45 (22, 101)	5,151 (24.3%)	7,340 (34.6%)	8,717 (41.1%)	15,775 (64.5%)
Other							
Duloxetine hydrochloride	3,947 (1.5%)	132 (3.3%)	42 (24, 91)	36 (27.3%)	46 (34.8%)	50 (37.9%)	601 (2.5%)
Flupentixol dihydrochloride	1,498 (0.6%)	188 (12.6%)	35 (21, 63)	60 (31.9%)	76 (40.4%)	52 (27.7%)	92 (0.4%)
Mirtazapine	10,581 (4.0%)	1,152 (10.9%)	35 (17, 76)	258 (22.4%)	516 (44.8%)	378 (32.8%)	3,958 (16.2%)
Venlafaxine hydrochloride	1,854 (0.7%)	176 (9.5%)	36 (17, 79)	54 (30.7%)	67 (38.1%)	55 (31.2%)	1,367 (5.6%)
Other	59 (<0.1%)	10 (16.9%)	23 (10, 40)	2 (20.0%)	6 (60.0%)	2 (20.0%)	51 (0.2%)
Total other AD	17,939 (6.8%)	1,658 (9.2%)	35 (18, 74)	410 (24.7%)	711 (42.9%)	537 (32.4%)	6,069 (24.8%)
All AD products (n=262,844)		24,471 (9.3%)	44 (22, 98)	5,969 (24.4%)	8,688 (35.5%)	9,814 (40.1%)	

[a] Within each AD class, medications accounting for >0.5% of first line ADs were grouped together to form an 'other' category

Firstline: the index antidepressant; secondline: the second prescribed antidepressant

Table 2: Pattern of AD switching according to drug class (percentage of those who have switched, n= 24,471)

	Second line treatment		
	TCA	SSRI	Other
First line treatment			
TCA	163 (0.7%)	1,210 (4.9%)	232 (0.9%)
SSRI	2,282 (9.3%)	13,235 (54.1%)	5,691 (23.3%)
Other	182 (0.7%)	1,330 (5.4%)	146 (0.6%)
All AD	2,627 (10.7%)	15,775 (64.5%)	6,669 (24.8%)

Table 3: Characteristics associated with AD switching

	First line SSRI	First line TCA	First line other AD	Switched AD	Did not switch AD	OR (95%CI)	P value
Gender							
Females	142,964 (84.8%)	13,662 (8.1%)	11,938 (7.1%)	14,699 (8.7%)	153,865 (91.3%)	Reference	
Males	85,488 (90.7%)	2,791 (2.9%)	6,001 (6.4%)	9,772 (10.4%)	84,508 (89.6%)	1.21 [1.18, 1.24]	<0.001
Age							Omnibus P for age <0.001
<18	4,219 (92.6%)	220 (4.8%)	117 (2.6%)	306 (6.7%)	4,250 (93.3%)	0.66 [0.59, 0.74]	<0.001
18-30	48,474 (92.9%)	1,615 (3.1%)	2,098 (4.0%)	5,000 (9.6%)	47,187 (90.4%)	0.97 [0.94, 1.01]	0.153
31-45	66,133 (90.3%)	3,521 (4.8%)	3,548 (4.9%)	7,191 (9.8%)	66,011 (90.2%)	1.00	-
46-60	56,310 (86.0%)	4,496 (6.9%)	4,642 (7.1%)	6,286 (9.6%)	59,162 (90.4%)	0.98 [0.94, 1.01]	0.170
61-75	30,710 (80.2%)	3,754 (9.8%)	3,837 (10.0%)	3,454 (9.0%)	34,847 (91.0%)	0.91 [0.87, 0.95]	<0.001
76+	22,606 (77.5%)	2,847 (9.8%)	3,697 (12.7%)	2,234 (7.7%)	26,916 (92.3%)	0.76 [0.73, 0.80]	<0.001
History of self-harm							
No	214,820 (86.9%)	15,540 (6.3%)	16,788 (6.8%)	22,439 (9.1%)	224,709 (90.9%)	Reference	
Yes	13,632 (86.9%)	913 (5.8%)	1,151 (7.3%)	2,032 (13.0%)	13,664 (87.0%)	1.49 [1.42, 1.56]	<0.001
Past year self-harm							
No	226,167 (86.9%)	16,387 (6.3%)	17,708 (6.8%)	24,186 (9.3%)	236,076 (90.7%)	Reference	
Yes	2,285 (88.5%)	66 (2.6%)	231 (8.9%)	285 (11.0%)	2,297 (89.0%)	1.21 [1.07, 1.37]	0.002
History of psychiatric illness							
No	61,659 (81.2%)	6,821 (9.0%)	7,418 (9.8%)	4,230 (5.6%)	71,668 (94.4%)	Reference	
Yes	166,793 (89.2%)	9,632 (5.2%)	10,521 (5.6%)	20,241 (10.8%)	166,705 (89.1%)	2.06 [1.99, 2.13]	<0.001
History of depression							
No	76,645 (82.1%)	8,372 (9.0%)	8,329 (8.9%)	5,699 (6.1%)	87,647 (93.9%)	Reference	
Yes	151,807 (89.5%)	8,081 (4.8%)	9,610 (5.7%)	18,772 (11.1%)	150,726 (88.9%)	1.92 [1.86, 1.98]	<0.001
History of anxiety							
No	146,208 (86.4%)	10,894 (6.4%)	12,192 (7.2%)	13,457 (7.9%)	155,837 (92.1%)	Reference	
Yes	182,244 (87.9%)	5,559 (5.9%)	5,747 (6.1%)	11,014 (11.8%)	82,536 (88.2%)	1.54 [1.50, 1.59]	<0.001